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Original Article

Pulmonary function outcomes for assessing cystic fibrosis care

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Abstract

Background: Assessing cystic fibrosis (CF) patient quality of care requires the choice of an appropriate outcome measure. We looked systematically and in detail at pulmonary function outcomes that potentially reflect clinical practice patterns.
Methods: Epidemiologic Study of Cystic Fibrosis data were used to evaluate six potential outcome variables (2002 best FVC, FEV_1, and $FEF_{25–75}$ and rate of decline for each from 2000 to 2002). We ranked CF care sites by outcome measure and then assessed any association with practice patterns and follow-up pulmonary function.
Results: Sites ranked in the top quartile had more frequent monitoring, treatment of exacerbations, and use of chronic therapies and oral corticosteroids. The follow-up rate of pulmonary function decline was not predicted by site ranking.
Conclusions: Different pulmonary function outcomes associate slightly differently with practice patterns, although annual FEV_1 is at least as good as any other measure. Current site ranking only moderately predicts future ranking.

Keywords: Benchmarking; Cystic fibrosis; Lung function; Outcomes; Clinical care

1. Introduction

Much has been written in recent years about improving quality of care for patients with cystic fibrosis (CF) [1–8]. Evidence points to improved patient outcomes associated with the development of quality improvement processes in CF care sites [9,10], and benchmarking efforts in both the United States and Germany have identified structural factors and care processes within care sites that are associated with improved patient outcomes [4,6]. Ideally one would like to know which therapies or practices result in better patient outcomes. Given the increasing number of therapies for treating CF, comparative effectiveness studies looking at real world use of multiple different therapies are needed to counter the tendency to place every patient on every therapy proven beneficial by randomized controlled trials. However, benchmarking and comparative effectiveness studies are influenced by the choice of outcome. Different care sites may be identified as top performing, depending on whether one chooses survival as the outcome or chooses to focus on pulmonary, nutritional, or quality-of-life outcomes.

Since pulmonary function is most closely related to patient survival, we designed this study to look systematically at several baseline spirometric measures of pulmonary function that might be clinically useful and meaningful as indicators of respiratory outcomes in CF, and to see how closely these measures are associated with clinical practice patterns. Johnson

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et al. [11] reported on a study dividing care sites into quartiles based on the average forced expiratory volume in 1 s (FEV_1) percent predicted (%pred) and then compared care practices in upper and lower quartile sites. Although FEV_1 at a single time has been used historically as a surrogate for long-term pulmonary outcome and to assess mortality risk [12,13], other pulmonary function measures, such as forced vital capacity (FVC) and forced expiratory flow at mid-lung volume ($FEF_{25–75}$), might be more predictive depending on the severity of a patient's lung disease. Furthermore, rate of decline may be a more appropriate measure than a single value at one point in time [14,15].

We analyzed several approaches for determining site rankings. First we looked cross-sectionally at three pulmonary function measures: FVC, FEV_1, and $FEF_{25–75}$. Then we examined patient-specific rate of decline in lung function for each of these measures. Finally, to determine whether site ranking based on any of these pulmonary function measures is predictive of future pulmonary or nutritional outcomes, we compared patient-specific lung function rate of decline and weight for age or body mass index (BMI) rate of decline at upper and lower quartile sites for the 2 years following the initial site ranking. We also evaluated if there was any association between the site ranking and care patterns over this follow-up period.

2. Methods

We used data from the Epidemiologic Study of Cystic Fibrosis (ESCF), a multicenter, encounter-based observational study designed to characterize the natural history of patients with CF in North America [16], to develop site quartiles based on different measures of pulmonary function and to determine whether the use of specific CF therapies was associated with better site outcomes using an approach similar to that of Johnson et al. [11]. Informed consent was obtained according to the policies governing research at each participating institution.

We included data from 2000 to 2004 and divided patients into three groups based on their ages at the end of 2002 (6–12, 13–17, and 18+ years). To be included in the data for site rankings, each patient needed ≥ 1 spirometry in 2000, ≥ 1 in 2001, and ≥ 1 in 2002. Site quartiles were developed for each of six variables: best recorded value during 2002 for FVC, FEV_1, and $FEF_{25–75}$; and change from the best percent predicted value in 2000 to the best in 2002 (rate of decline) for FVC, FEV_1, and $FEF_{25–75}$. Annualized rates of decline took account of the dates of the best values and divided the difference in values by the time in years. Percent predicted values were calculated using reference equations from Wang et al. [17] through age 15 for girls and age 17 for boys and Hankinson et al. [18] for older patients.

Each site had to have participated in ESCF from 2000 to 2004 and had to have at least 10 eligible patients within an age group to receive a quartile assignment for that age group. Median values of each of the 6 measures for each of the 3 age groups were calculated for all eligible sites (up to 18 possible values per site). Sites were classified for each age group based on the median value for each measure.

After creating the site quartile variables (based on data from 2000 to 2002), we assessed the association between these quartile assignments and patient care patterns during 2002. Additionally we looked for any associations between these quartile assignments and follow-up care patterns and outcomes from 2002 to 2004. Patients were included in this analysis if they belonged to a site with at least one quartile assignment and had at least one visit and at least one spirometry in each year 2002, 2003, and 2004. Patient care patterns and outcome variables were analyzed within the three age groups.

Practice patterns evaluated for association with quartile ranking were healthcare use (4), use of chronic therapies (9), hospitalization and treatment of exacerbations (7), and nutritional status (2) (Tables 1, 2). We evaluated both 1-year values (2002) and 3-year values (2002 to 2004) for these practice patterns to assess associations with site pulmonary function quartiles. We also assessed the association between site ranking quartiles in 2002 and future pulmonary function outcomes from 2002 to 2004.

Patients from sites in the highest quartile were compared to patients from sites in the lowest quartile on these practice patterns and pulmonary function outcome measures. Comparisons were stratified by each patient's highest FEV_1 %pred in 2002 (<40, 40–69, 70–99, ≥ 100) so that patients with a similar stage of lung disease were compared regardless of their site's quartile. Patients, stratified by disease stage, at the highest and lowest quartile sites were compared using stratified Wilcoxon rank sum tests (for continuous outcome variables) and Mantel-Haenszel tests (for categorical outcome variables). No adjustment was made for multiple comparisons. Site rankings were compared using Spearman's rank correlation. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

3. Results

Data from 7729 patients were ranked by pulmonary function test outcomes in 2002, including 2033 age 6–12 years (85 sites), 2129 age 13–17 years (85 sites), and 3567 age 18 years or older (109 sites).

Associations between outcomes and practice patterns recorded in 2002 are shown in Table 1. The left column lists the processes considered, and the right columns represent the association with site quartiles ranked by average 2002 pulmonary function or by change in pulmonary function from 2002 to 2004. The right columns are divided by the spirometry value analyzed (FVC %pred, FEV_1 %pred, $FEF_{25–75}$ %pred) and subdivided into age groups. Practice patterns associated with a positive site ranking (i.e. more likely to occur in upper quartile sites) are shown as either a single + ($p < 0.05$) or a double ++ ($p < 0.001$); those negatively associated with site ranking (less likely to occur in upper quartile sites) are shown as either a single − ($p < 0.05$) or a double − − ($p < 0.001$).

As an example, there are strong associations ($p < 0.001$) between site quartile as determined by the average $FEF_{25–75}$ %pred in 2002 for the group age 6–12 years and the numbers of clinic visits, spirometries, and respiratory tract cultures and the likelihood of obtaining at least one respiratory tract culture during the year. If instead we use the change in $FEF_{25–75}$ %pred from 2000 to 2002 as

Table 1
Associations among 2002 healthcare use, chronic therapies, hospitalization and treatment of pulmonary exacerbations, and nutritional status with site quartiles using different pulmonary function outcomes in different age groups.

	2002									2000–2002 change								
	FVC			FEV_1			$FEF_{25–75}$			FVC			FEV_1			$FEF_{25–75}$		
Age group, years	**6–12**	**13–17**	**18+**	**6–12**	**13–17**	**18+**	**6–12**	**13–17**	**18+**	**6–12**	**13–17**	**18+**	**6–12**	**13–17**	**18+**	**6–12**	**13–17**	**18+**
Healthcare use in 2002																		
No. of visits			+	+			++		+									
No. of spirometries		+	++	++		++	++	++	+									
No. of respiratory tract cultures	++	++	++	++	++	++	++	++	++		++	+	++	+		+		
Any respiratory tract culture	++	+	++	++	+	++	++	++	++	++	+	+	++			++		+
Chronic therapies in 2002																		
Inhaled antibiotics			+			+				−				+			++	
Non-quinolone oral antibiotics	++	+	++	+	++	+		++									+	
Mast cell stabilizers	+		++	++		++	+		++		−	++	−	−		+		−
Inhaled corticosteroids						−				−	−			+			+	+
Oral corticosteroids	++	++	++	++	++	++		++	++								++	
Inhaled bronchodilators			−		−			−		−							++	+
Dornase alfa						++	++		+							− −		
Pancreatic enzymes			+			+			+									−
Airway clearance techniques			−															++
Hospitalization and treatment of exacerbation in 2002																		
No. of hospitalizations		+								+	+	+	+	+			+	
No. of IV antibiotic treatments for exacerbations							+						+			−		
Any IV antibiotic treatment for exacerbations			+				+						+					
No. of inhaled antibiotic treatments for exacerbations	++	++	++	++	+	++		+	++	+	+			−		− −		
Any inhaled antibiotic treatment for exacerbations	++	++	++	++	+	++		+	++	+	+			−	− −			
No. of oral quinolone treatments for exacerbations											+							
Any oral quinolone treatment for exacerbations											+							+
Nutritional status in 2002																		
Highest weight-for-age percentile																		
Highest BMI-for-age percentile				+														

BMI, body mass index; $FEF_{25–75}$, forced expiratory flow at mid-lung volume; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; IV, intravenous.
++ indicates $p < 0.001$ in positive direction.
+ indicates $p < 0.05$ in positive direction.
− indicates $p < 0.05$ in negative direction.
− − indicates $p < 0.001$ in negative direction.
Positive direction means higher rankings (upper vs lower quartile) are associated with more of the healthcare measure.
Negative direction means higher rankings (upper vs lower quartile) are associated with less of the healthcare measure.

Table 2
Associations between 2002 and 2004 follow-up healthcare use, chronic therapies, hospitalization and treatment of pulmonary exacerbations, nutritional status, and pulmonary function with site quartiles using different pulmonary function outcomes in different age groups.

	2002									2000–2002 change								
	FVC			FEV_1			$FEF_{25–75}$			FVC			FEV_1			$FEF_{25–75}$		
Age group, years	6–12	13–17	18+	6–12	13–17	18+	6–12	13–17	18+	6–12	13–17	18+	6–12	13–17	18+	6–12	13–17	18+
Healthcare use during 2002–2004																		
No. of visits			++	+		++	++		++			++	+		+			+
No. of spirometries	+	+	++	++		++	++	++	++			+						++
No. of respiratory tract cultures	++	++	++	++	++	++	++	++	++		++	++	++			+		+
Any respiratory tract culture	+	+		+	+			+		+						+		
Chronic therapies during 2002–2004																		
Inhaled antibiotics						+	−			−				+			++	
Non-quinolone oral antibiotics	++	++	+	+	++	+		++			−				− −		+	−
Mast cell stabilizers	+		++	++		++	+		++		−	++	−			+		−
Inhaled corticosteroids						−		+		−	−	+		++		−	++	++
Oral corticosteroids	++	++	++	++	++	++		++	++		−					− −	++	
Inhaled bronchodilators							+										++	+
Dornase alfa						++	++		++		−					− −		
Pancreatic enzymes			+			+			+								+	
Airway clearance techniques													+				+	+
Hospitalization and treatment of exacerbation during 2002–2004																		
No. of hospitalizations		+								+	+	−	+	+				
No. of IV antibiotic treatments for exacerbations		+		+			+					−	−	+				
Any IV antibiotic treatment for exacerbations		+	+	+		+				+			++	+				
No. of inhaled antibiotic treatments for exacerbations	++	++	++	++	+	++	+	+	+	++		++		−	+	− −		
Any inhaled antibiotic treatment for exacerbations 4	++	++	++	++	+	++	+			++		++	+		+	− −		
No. of oral quinolone treatments for exacerbations	++		+	++						++		++	++		++	−		+
Any oral quinolone treatment for exacerbations				++	−					++			++		++	+		++
Nutritional status during 2002–2004																		
Slope weight-for-age percentile			− −						−		−							
Slope BMI-for-age percentile			−	− −					−									
Pulmonary function during 2002–2004																		
Slope FEV_1 %pred	+													−	− −			
Slope FVC %pred	+	−										−			−	+		
Slope $FEF_{25–75}$ %pred		−					−								−			−

BMI, body mass index; $FEF_{25–75}$, forced expiratory flow at mid-lung volume; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; IV, intravenous.
++ indicates $p < 0.001$ in positive direction.
+ indicates $p < 0.05$ in positive direction.
− indicates $p < 0.05$ in negative direction.
− − indicates $p < 0.001$ in negative direction.
Positive direction means higher rankings (upper vs lower quartile) are associated with more of the healthcare measure.
Negative direction means higher rankings (upper vs lower quartile) are associated with less of the healthcare measure.

Table 3
Spearman correlations of site rankings.

			2002									2000–2002								
			FVC			FEV_1			$FEF_{25–75}$			FVC			FEV_1			$FEF_{25–75}$		
Age group, years			6–12	13–17	18+	6–12	13–17	18+	6–12	13–17	18+	6–12	13–17	18+	6–12	13–17	18+	6–12	13–17	18+
2002	FVC	6–12																		
		13–17	0.66																	
		18+	0.48	0.62																
	FEV	6–12	0.87	0.75	0.44															
		13–17	0.69	0.88	0.49	0.76														
		18+	0.47	0.61	0.86	0.47	0.52													
	FEF	6–12	0.57	0.65	0.32	0.75	0.66	0.36												
		13–17	0.60	0.74	0.46	0.71	0.86	0.52	0.61											
		18+	0.32	0.48	0.62	0.39	0.39	0.83	0.34	0.44										
2000–2002	FVC	6–12	0.49	0.32	0.15	0.48	0.30	0.13	0.37	0.30	0.09									
		13–17	0.28	0.36	0.08	0.26	0.36	0.06	0.22	0.38	−0.06	0.61								
		18+	0.30	0.26	0.25	0.31	0.27	0.18	0.26	0.23	0.06	0.35	0.31							
	FEV	6–12	0.53	0.27	0.11	0.49	0.26	0.08	0.31	0.27	0.01	0.86	0.63	0.33						
		13–17	0.37	0.33	0.08	0.26	0.36	0.08	0.21	0.37	−0.02	0.53	0.78	0.28	0.57					
		18+	0.27	0.15	0.12	0.29	0.19	0.05	0.22	0.09	−0.02	0.29	0.18	0.75	0.34	0.22				
	FEF	6–12	0.26	0.22	0.08	0.29	0.21	0.05	0.23	0.23	0.02	0.38	0.33	0.21	0.44	0.46	0.13			
		13–17	0.28	0.14	−0.06	0.14	0.19	−0.06	0.07	0.35	−0.09	0.30	0.42	0.16	0.32	0.57	0.09	0.30		
		18+	0.03	−0.06	−0.12	−0.05	0.00	−0.09	0.01	−0.02	−0.06	0.04	−0.05	0.13	0.07	0.18	0.49	0.09	0.20	

$FEF_{25–75}$, forced expiratory flow at mid-lung volume; FEV , forced expiratory volume in 1 second; FVC, forced vital capacity.
Number of sites ranges from 70 to 85 for all comparisons except the 18+ age group with 18+ age group comparisons, in which case the number of sites is 109.
Dark shading indicates correlations ≥0.60 and light shading indicates correlations 0.40 to <0.60 (breakpoints chosen arbitrarily to aid in discussion).

the ranking criterion, the only associations found are with the number of respiratory tract cultures ($p < 0.05$) and the likelihood of obtaining at least one respiratory tract culture ($p < 0.001$).

Overall analysis of Table 1 suggests that sites using more frequent monitoring (spirometries, respiratory cultures), more chronic therapies (particularly oral corticosteroids, mast cell stabilizers, and non-quinolone antibiotics), and more frequent inhaled antibiotics when treating exacerbations tended to be in the higher quartile irrespective of the 2002 pulmonary function measure. When rate of decline was used for ranking, only the frequency of respiratory cultures and number of hospitalizations were associated with higher quartile sites across different age groups and pulmonary function measures.

Associations between outcomes and practice patterns recorded from 2002 to 2004 are shown in Table 2. Again, rankings were based on average pulmonary function in 2002 or change in pulmonary function from 2000 to 2002 and were separated by pulmonary function test and age group. As might be expected, higher quartile sites with rankings based on 2002 data tended to continue more frequent monitoring, treat more exacerbations, and use more oral corticosteroids from 2002 to 2004. There is essentially no positive association between the site ranking in 2002 (either by average pulmonary function or by change from 2000 to 2002) and the pulmonary function or nutritional outcomes during the follow-up 2 years. In fact, there was a negative association between 2002 ranking for FVC in 18+-year-olds and change in weight-for-age and BMI percentiles. There was also a negative association with change in BMI percentile for 6- to 12-year-olds in sites ranked by 2002 FEV_1. For lung function outcomes, follow-up FEV_1 was more likely to decline from 2002 to 2004 in sites ranked more highly (for 13- to 17-year-olds and 18+-year-olds) based on change in FEV_1 from 2000 to 2002.

As expected there were moderate to strong correlations between site rankings based on FVC, FEV_1, and $FEF_{25–75}$ measured in 2002 (Table 3). The highest correlations were between FVC and FEV_1 and between FEV_1 and $FEF_{25–75}$ within age group (0.75–0.88), with high correlations also seen within and across measures between the 6- to 12-year-olds and the 13- to 17-year-olds (0.60–0.76). However, the correlation of rankings by cross-sectional measures with rankings by rate of decline was low (≤0.38) except for FEV_1 and FVC for 6- to 12-year-olds (0.48–0.53).

Site rankings were moderately stable from 2002 through 2004 (Table 4). Correlations ranged from 0.51 to 0.80 between 2002 and 2003 or 2004. The percentage of sites that remained in the same quartile during both 2003 and 2004 was 30% to 50% for the upper quartile and 33% to 60% for the lower quartile.

4. Discussion

Benchmarking is a process by which individual or organizational performance at the highest level may be identified for

Table 4
Site rankings in 2002, 2003, and 2004.

Age group, years		Spearman correlation (no. sites)		Upper quartile,[a] %			Lower quartile,[b] %		
2002	2002	2003	2004	2003	2004	2003 and 2004	2003	2004	2003 and 2004
FVC	6–12	0.61 (72)	0.72 (66)	60	55	50	41	65	35
	13–17	0.68 (68)	0.71 (71)	70	55	45	53	76	35
	18+	0.62 (81)	0.66 (84)	62	62	48	67	73	60
FEV	6–12	0.72 (72)	0.67 (66)	63	54	50	53	53	35
	13–17	0.80 (68)	0.61 (71)	55	50	35	72	50	44
	18+	0.74 (81)	0.68 (84)	61	52	43	53	53	53
FEF	6–12	0.56 (72)	0.51 (66)	52	43	38	60	53	33
	13–17	0.71 (68)	0.61 (71)	50	45	30	56	63	56
	18+	0.72 (81)	0.60 (84)	63	59	41	75	65	60

$FEF_{25–75}$, forced expiratory flow at mid-lung volume; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

[a] Percentage of upper quartile sites in 2002 that were also upper quartile sites in 2003, 2004, and in both 2003 and 2004.

[b] Percentage of lower quartile sites in 2002 that were also lower quartile sites in 2003, 2004, and in both 2003 and 2004.

purposes of comparison and goal setting. We designed this study to look systematically at several clinically useful pulmonary function measures and see how well these measures correlated with care practices, potentially identifying their value for benchmarking. Additionally we wanted to see if any of several methods for ranking sites would have better longitudinal correlation. Patient-specific cross-sectional pulmonary function (FEV_1) proved to have a greater number of significant associations across age groups and healthcare measures than rate of decline using FVC, FEV_1, or $FEF_{25–75}$. Although all pulmonary function measures demonstrated some association with care practices, FEV_1 appeared to have more associations in all age groups. We found minimal association between site ranking in 2002 and follow-up pulmonary function rate of decline. Additionally, while site ranking in 2002 was moderately associated with future site rankings, no more than half of the upper quartile sites remained in the upper quartile during both 2003 and 2004.

One goal of this analysis was to examine the hypothesis that longitudinal change in lung function (rate of decline) would be a better reflection of treatment by CF care sites than a single cross-sectional pulmonary function value. In general, however, the 2002 single year rankings were more likely to be associated with frequency of monitoring, use of chronic therapies, and treatment of exacerbations compared to the rate of decline rankings. From a single patient perspective, this finding may seem counterintuitive because one would expect that a patient receiving more therapies might show a lower rate of decline. We have previously shown that patients with higher baseline pulmonary function are more likely to experience more rapid rates of decline than patients with lower pulmonary function, and that this may be due to less aggressive treatment [14,19]. This greater decline for patients with high FEV_1 may contribute to a greater decline in average lung function for sites with a large number of patients who have high pulmonary function. Another contributing factor may be regression to the mean, in which sites in the extreme quartiles tend to have less extreme pulmonary function results the next year as they regress toward the mean of all sites. This might result in little association between greater use of therapies by high quartile sites and change in pulmonary function.

Additionally, we wanted to determine how different pulmonary function measures identified top performing sites. The use of $FEF_{25–75}$ for ranking had the best association with monitoring in the younger age groups, whereas there was no difference between pulmonary function measures in the adult group. Given that CF-related lung disease appears first in the small airways, this association with $FEF_{25–75}$ (a measure of smaller airway function) in younger patients seems reasonable [20]. However, patients with CF experience their most dramatic declines in pulmonary function during their adolescent years. By the time they reach adulthood, airway disease is more advanced and impacts the larger airways [21]. Consistent with greater involvement of large airways, both FVC and FEV_1 appear to be more closely associated with inhaled antibiotic treatment of pulmonary exacerbations.

Another goal was to determine whether site ranking during 1 year would be predictive of practice patterns and pulmonary function or nutrition outcomes during the next 2 years. During the 5 years studied, associations with monitoring and therapies before ranking were similar to those after the ranking year. Follow-up changes in nutritional status and pulmonary function were only minimally associated with site rankings. For an individual patient this suggests that while high lung function predicts more rapid decline [14], being cared for in a high-ranking site does not predict less decline. Although one would like to think high site rank is attributable to practice patterns that result in continued superior outcomes, this finding suggests appreciable variation over time. In fact, ranking by highest pulmonary function in 2002 had only a moderate, but not strong, correlation with rankings in 2003 and 2004, with no more than half the upper quartile sites maintaining this ranking for the next 2 years.

In general, our results show that some practice patterns consistently track with higher site rankings and others do not. This reflects the findings of Schechter et al. [5,22,23] when they benchmarked high-performing CF care sites in the United States. They found above average, but not remarkably high, use of chronic therapies in these sites and above average, but not remarkably better, nutritional outcomes. They also found that a variety of factors not normally monitored, such as strength and leadership of the care team, were predictors of better outcomes. Unfortunately, ESCF does not have data on these structural clinic factors.

The only clinical practice pattern consistently associated with upper quartile sites was the number of respiratory tract cultures. It is unclear whether this may indicate that early detection and

intervention to control or eradicate bacteria produce better outcomes, given the lack of association with frequency of anti-pseudomonas treatment. It does suggest, however, that close monitoring is performed in care sites with better outcomes, as reported by Johnson et al. [11].

Two consistent findings regarding chronic therapies were related to anti-inflammatory medications. Upper quartile sites showed greater use of oral, but not inhaled, corticosteroids in all age groups and greater use of mast cell stabilizers, especially in adults. Given that airway inflammation is central to disease progression in patients with CF, patients at these sites may be realizing a benefit from anti-inflammatory therapy [24]. Generally, however, these therapies are used infrequently, and their use has been decreasing over time [25]. In ESCF the use of oral corticosteroids is recorded only as a chronic therapy and likely does not include intermittent use. Another potential anti-inflammatory therapy is inhaled corticosteroids, but the use of this medication had no association with ranking outcomes. Unfortunately, we did not have enough data to evaluate the use of ibuprofen or azithromycin, two other anti-inflammatory therapies for CF. Although anti-inflammatory therapies have been shown to be effective in CF and may well explain this association, their use may simply be a marker of more aggressive treatment [26,27].

Nutritional status in 2002 and change in nutritional status from 2002 to 2004 showed little association with quartile ranking by pulmonary function. In young patients with CF, nutritional status is associated with future lung function, and in older patients, lower lung function occurs predominantly in those who are malnourished; therefore, the lack of association between ranking in 2002 and follow-up nutritional status is disappointing [28,29]. However, it may be that ranking sites by patient nutritional status rather than by pulmonary function is more predictive of future nutritional or lung health.

Site rankings in 2002 correlated with all three measures of pulmonary function but not rate of decline. Given that FVC, FEV_1, and $FEF_{25–75}$ all derive from the same pulmonary function test and are related to each other, it is not surprising that site rankings based on these measures would show similarities.

In performing our analyses we did not adjust for case mix as is sometimes done when benchmarking CF care sites. We believe the first goal in benchmarking is to identify whether an outcome discriminates between care sites and whether the outcome reflects an aspect of interest (in this case care practice patterns). This is the approach followed in the past when developing CF outcomes for benchmarking. We do believe that before validating measures for benchmarking it will be important to case-mix adjust for various patient characteristics, such as socioeconomic and insurance status, to evaluate whether site difference in patient populations might impact the conclusions.

Finally, we were interested in how site rankings in 2002 compared with rankings in 2003 and 2004. No more than half the upper quartile sites were in the upper quartile for both 2003 and 2004 by any measure. This lack of stability suggests that quartile rankings based on spirometry results may be an imperfect measure of overall site quality. Potential reasons for this include patients changing age groups, patients changing sites, and the inherent variability in sites with few patients in a given age group.

As with any epidemiologic study, there are limitations to how these findings should be applied. Although there have been few new therapies for CF developed since this data was collected, practice patterns have likely changed over the past decade. One example is the use of corticosteroids, where current use may have decreased following studies showing little value [30]. A second example is the use of ibuprofen, a therapy seldom used during the time of this study [31]. It is important to realize that our findings do not define how a specific measure should be used, or not used, for benchmarking. Instead they identify patterns of interest between care practices and outcome measures.

5. Conclusions

The first step in benchmarking is to identify the outcome measure on which to compare sites. In this study we looked at 6 potential clinically useful measures in 3 age groups and found that although choice of pulmonary function for ranking changes associations slightly, in general the best FEV_1 during a single year is as good as or better than other measures for predicting future lung function. Pulmonary function serves as a surrogate for mortality risk, which suggests that ranking by pulmonary function indirectly ranks mortality risk [32,33]. We found that looking at rate of decline to define top performing sites had no benefit over a single measure and that subsequent rate of decline was not associated with site ranking by previous pulmonary function. One of the most consistent findings in this study, and in the study by Johnson et al. [11], was that better pulmonary outcomes were associated with close monitoring, as evidenced by culture and clinic visit frequency. In contrast, therapies other than oral corticosteroids and inhaled antibiotics have little association with average pulmonary function in a care site, so it appears that variables other than the use of chronic therapies are likely to explain much of the variation between sites [5,22].

Contributor's statement page

All authors attest to the following roles in the preparation of this manuscript:

(1) Substantial contributions to conception and design, acquisition of data or analysis and interpretation of data: Jeffrey S. Wagener, Eric P. Elkin, David J. Pasta, Michael S. Schechter, Michael W. Konstan, Wayne J. Morgan
(2) Drafting the article or revising it critically for important intellectual content: Jeffrey S. Wagener, Eric P. Elkin, David J. Pasta, Michael S. Schechter, Michael W. Konstan, Wayne J. Morgan
(3) Final approval of the version to be published: Jeffrey S. Wagener, Eric P. Elkin, David J. Pasta, Michael S. Schechter, Michael W. Konstan, Wayne J. Morgan

Conflict of interest statement

This study was sponsored by Genentech, Inc. Jeffrey Wagener, Michael Schechter, Michael Konstan, and Wayne Morgan have previously received honoraria from Genentech for serving as members of the North American Scientific Advisory Group for the Epidemiologic Study of Cystic Fibrosis, and their respective institutions previously received grant support from Genentech, Inc., for participating in the study. Jeffrey Wagener, Michael Schechter, Michael Konstan, and Wayne Morgan have served as consultants for Genentech. No compensation was provided to these authors in exchange for production of this manuscript. Jeffrey Wagener was previously an employee of Genentech, Inc. Eric Elkin and David Pasta are employees of ICON Clinical Research, which was paid by Genentech for providing analytical services for this study. The decision to submit the manuscript was made by the authors and was approved by Genentech, Inc.

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